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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/581,976 | 06/20/00 | DALEMANS W | B45124 |

020462 HM22/0828
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| EXAMINER | |
|---|---|
| LI,B | |
| ART UNIT | PAPER NUMBER |
| 1648 | 10 |

DATE MAILED: 08/28/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/581,976 | Applicant(s) DALEMANS ET AL. | |
|---|---|---|---|
| | Examiner Bao Qun Li | Art Unit 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 June 2001* .

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Response to Amendment*

This is response to the amendment C, paper No. 9, filed June 10, 2001. Amended specification and claims 1-5, 7-9 and 15-16 are entered. New claims 17-20 are added. Claims 1-11 and 13-20 are pending.

Please note any ground of rejection that has not been repeated is removed.

The text of those sections of Title 35, U.S. code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112*

Claims 1-2 and 15 are rejected under 35 USC § 112, second paragraph, on the same grounds as previously stated in the office action mailed 01/26/01. Applicants argue that the term of "optional link" is clearly set in the specification and the claims are also amended to overcome the rejection. Applicants' argument is respectfully considered, however, it is not found persuasive. Since the term of "optionally linked to" does not necessarily mean that the E6 or E7 fusion protein is linked to other immunogenic fusion partner that provide a T cell helper epitope. Therefore, the claims will read on some prior art that use E6 or E7 or E6/E7 fusion protein as the immunogenic composition as taught by Edwards (WO 06/19496). Applicants need to amend the claims to overcome the rejection.

### Claim Rejections - 35 USC § 103

Claims 1-11 and 13-16 are rejected under 35 USC § 112, second paragraph, on the same grounds as previously stated in the office action mailed 01/26/01. Applicants argue that the recited prior art does not suggest the need of improvement of HPV antigenicity can be achieved with combination of HPV antigen with CpG motif in the immunogenic composition. Therefore the rejection should be withdrawn. Applicants' argument is respectfully considered, however, it is not found persuasive. Since the term of "optionally linked to" does not necessarily mean that the E6 or E7 fusion protein is linked to other immunogenic fusion partner that provide a T cell helper epitopes, the claims will read on the prior art that use E6 or E7 or E6/E7 fusion protein as the immunogenic composition as taught by Edwards (WO 06/19496). Furthermore,

Boursenell et al. clearly teaches the same mutations that have been described in the specification of the instant Applicant and demonstrates that the composition comprising such mutated HPV antigen can significantly induce an immune response. This does not mean that the antigenicity of the PHV does not need to be improved because Boursenell et al. concludes that this results of the cited document described just the construction and characterization of a modified forms of E6 and E7 protein that are capable of inducing an HPV-specific CTL response with less neurovirulent than the parental virus and the goal of their work is to develop an agent that can induce an aggressive anti-tumor response against cervical cancer caused by HPV infection. This is a strong suggestion and motivation for any ordinary skill person in the art to seek some improvement for enhancing the primary immune response made by the safer and capable HPV antigen E6 and E7 in the field. Therefore, when oligonucleotide containing CpG motif has been discovered as an adjuvant, which can stimulate an immune response, especially it can redirect a Th2 response to a CTL Th1 response as taught by Chu et al. the motivation would have been become more obvious for any person skill in the art to combine the modified E6 and E7 antigen with an oligonucleotide containing CpG motif to see an enhanced immune response against the E6 or E7 primary HPV antigen without unexpected result. Therefore, the rejection is still remained and made **Final.**

**New Ground Rejection**

***Claim Rejections - 35 USC § 112***

Claims 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a variety of composition comprising E6 or E7 protein or E6/E7 fusion protein of HPV16 or HPV18 that is linked to the fusion partners plus an immunomodulatory oligodexynulceotide adjuvant that consists of CpG motif, wherein the said fusion partners consist of the protein D (Ser 20-Thr 127) of Heamophilius influenza B and the non-structural protein 1 (NS1) (4-81) of Influenza virus as well as a histidine residue or the bacterial Lyta motif of Strptococcus pneumonia (residue 188-305) and the NS1 (4-81) plus a histidine residue, and resulting in an enhanced Cytotoxic T cell Lysis (CTL) activity against E7/HPV16 antigen and partial tumor regression by co-administration of one construct (TCA308) consisting of E7 /HPV16 fused with protein D, NS1 sequence and histidine residues and an immunomodulatory CpG oligonucleotide (1826) into an E7 expressing tumor mouse model to

produce an immune response, does not reasonably provide enablement for having a method for preventing or treatment of HPV induced tumors in a patient by administering an effective amount of a composition comprising E6 or E7 protein or E6/E7 fusion protein in combination with an additional HPV antigen, such as L1 or L2 or E2 or E5 and CpG motif, wherein the E6 or E7 optionally linked with all kinds of fusion partner having a T helper epitope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the instant case, the specification discloses several compositions made from E6 or E7 or E6/E7 fusion protein of HPV16 of HPV18 linked with some fusion partners as described above [Prot-D1/3-E7-His/HPV16 (TCA308), Prot-D1/3-E6-His/HPV16 (TCA307), fusion Protein-D1/3-E6/E7-His/HPV16 (TCA311), clyta-E7-His/HPV16 (TCA330), clyta-E6-His/HPV16 (TCA332), clyta-E6/E7-His/HPV16 (TCA331), Prot-D1/3-E7-His/HPV18 TCA313), Prot-D1/3-E6-His/HPV18 (TCA314), Prot-D1/3-E7-His/HPV18 (TCA328)], wherein the E7 can be made by two point mutation as Prot-D1/3-E7matated (cys24→Gly, Glu26→Gln)-His/HPV16 (TCA347) or Prot-D1/3-E7matated (cys27→Gly, Glu29→Gln)-His/HPV18 (TCA355). But the specification only present that one composition comprising construct TCA308 in combination with an immunomodulatory oligonucleotide CpG No. 2 (1826) injected into the E7 expressing tumor mouse models, can result in an enhanced activity of Cytotoxic T Lymphocyte (CTL) against E7 antigen of HPV16, partial tumor regression and a weak antibody response. Applicants fail to teach whether the composition comprising E6 or E7 or E6/E7 plus an additional HPV antigen can produce any sustained immune response and prevent the tumor development.

Applicants are also remaindered that the field is unpredictable in that not every CpG motif can have such immunistimulating activity as evidenced by Yamamoto et al. (Immunobiology of Bacterial CpG-DNA, pp. 26-27, see the section 3.1 and 3.2). He teaches that although the hexamer palindromic sequences having -CG- motif are essential for inference (IFN) production and Nature Killer cell (NK) augmentation, some exceptional cases still exist. For instance, GTCGTT and GACGTT are active, and GACGTC is inactive (pp. 30, 2nd paragraph). It is also true that formula, purine purine cytosin quanine pyrimidine pyromidine (Pu-Pu-CG-Py-

Py), which has been used wildly by many investigations, has many exceptions (pp. 31, 2nd paragraph). Even in the present case, the specification only shows that 1 out of 3 such oligonucleotide exhibits some augmentation of the CTL activity against the E7/HPV16 antigen and partial tumor regression.

Especially considering the general and broad statements in the claims. With regard to an unpredictable field, this does not constitute an adequate disclosure. See Fiers v. Revel (25USPQ2d 1601 at 1606; and also decision by the Federal Circuit with regard to the enablement issues see Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001-1007). For example, the CAFC stated that "It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute enablement." (See page 1005 of the decision). In the instant case, the breadth and scope of claims read on prevention or treatment of tumor caused by HPV infection. Because the HPV infections tend to be a latent infection, in order to be able the invention, a sustained immune response and a completely prevention of HPV induced tumor development would be required. Applicants are reminded that the field of such therapeutic vaccine is highly unpredictable. Therefore, the disclosed results cannot be extrapolated to the long-term protection against HPV infection. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation. The applicant cannot rely on the knowledge of those skilled in the art to enable the claims without providing adequate teaching. Therefore, a person skill in the art would be required to do an undue experimentation to enable the full scope of the claimed invention.

As there is no clear teaching how the said compositions can induce a long-term immunity against any or all types of HPV infection and prevent the HPV induced tumor development, the lack of guidance for proper selection of the CpG oligonucleotide sequence which can enhance the immunity against any or all kinds of antigen from any types of the HPV, one of a skilled person in the art would be required to conduct large quantity of experimentation to enable the full scope of the claimed invention.

Therefore, considering large quantity of experimentation needed, the unpredictability of the field, the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim. Many of these factors have been summarized *In re Wands, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).*

***Claim Rejections - 35 USC § 103***

Claims 1, 7, 17 and 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gissmann et al. (U.S. Patent No. 6,228,368 B1) and further in view of Chu et al. (J. Exp. Med. 1997, Vol. 186, pp. 1623-1631).

The present Application is drawn to an mmunogenic compositioncomplrising a HPV E6 or E7 or E6/7 fusion protein optionally linked to a T helper epitioes and an additional HPV antigen selected from L1 or L2 or E1 or E5 as well as an oligonucleotide sequence containing CpG motif to induce an immune response in a host, wherein the aadtional of L1 or L2 protein of HPV make a viral like particle.

Gissmann et al. teaches a method for a antigen formulation and a method for making such antigen. The said antigen is a fusion protein of human papilloma virus (HPV) is initially produced in Sf9 insect cell system transfected with a recombinant baculovirus comprising sequence encoding the major coat protein L1 fused with secondary protein polypeptide other than 11 protein of HPV and processed as either a viral like particle (VLP) of HPV or capsomere of HPV. The VLP is further disassemblies as a capsmere by intact with EDTA overnight (clo. 13, lines 52-60). The said fusion protein comprises a truncated HPV L1 protein with a deletion of one or more amino acid residues from either C-terminal or N-terminal of the HPV L1 protein and an adjacent amino acid residue from second protein, wherein the said HPV virus is selected from the group consisting HPV6, HPV 11, HPV16, HPV 18 and the said secondary protein of HPV is an early HPV protein selected from the group consisting of E1, E2, E3, E4 E5, E6 and E7 (see claims 1-5, 9, 12-14). Although Gissmann et al. does not recite the HPV viral like particle in the claims, he teaches a method of how to make VLP of HPV with mutated L1 protein with other non-L1 protein in the Sf9 cells, indicating that the structure of the said HPV fusion protein maintains a native conformational epitope because the native conformational epitope is necessary element for producing a viral like particle for HPV. Gissmann et al also teaches that the said fusion protein antigen can be used to induce specific antibody and immunize mice (col. 15, lines 5-19), indicating that the said fusion protein of HPV VLP comprising an immunogenic epitope. Gissman does not teaches that the immune composition containing an oligonucleotide containing CpG motif to enhance the immune response.

Chu et al. taught that synthetic oligonucleotides comprising CpG motif (one of them is nucleotide 1826) acts as an adjuvant that enhance the Th1-dominated response to co-administrated antigen (see entire document). Although Chu did not use the E6 or E7 as a co-administrated antigen, but she clearly demonstrated that the synthetic oligonucleotides containing CpG motif are potential adjuvants for human vaccine to elicit protective Th1 immunity.

Taken together, the state of the art taught that the E6 or E7 of HPV16 and HPV18 has long been a well-characterized antigen known in the art for their property related to the cervical cancer development. The E7 antigen in combination with other HPV antigen have long been recognized and used as the target for developing CTL activity of Th1 type cellular immunity against E7 antigen in the art too. Some of the E6 or E7 fusion proteins have already been put into the clinical trials. The L1 or L2 protein of HPV cannot only provide an antigenicity to the immunity against HPV but also can constitute a viral like particle. The adjuvant consisting of immunomodulatory oligonucleotide CpG motif (or called immunostimulatory sequences ISS) having a strong immune stimulatory function as evidenced by Chu. Therefore, it is concluded that it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be amply motivated by the recited references to combine the method taught by Gissmann et al. and further in view of Chu et al. to make an immunogenic composition against the HPV infection without an unexpected result. Hence the claimed invention as a whole is considered to be prima facie obvious absence unexpected results.

No claims are allowed.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li

August 23, 2001

James C. Housel
JAMES HOUSEL 8/27/01
SUPERVISORY PATENT EXAMINER
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